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ETHYL CORPORATION

HEALTH & ENVIRONMENT DEPARTMENT

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DATE: December 18, 1991 — Page 1 of 8 Pages

TO: J. G. Smith — FAX #: Ethyl D.C.
K. L. Fast — FAX #: 202/778-2201

FROM: G. D. Pfeifer — TELEPHONE #: (504) 388-7565

Here are the expanded comments on solubility.

a-91-46

G. D. Pfeifer

GDP:cr
Attachments

A-91-46
IV-D-61

# ETHYL CORPORATION

Health and Environment Department

Air Conservation

Ethyl Tower
451 Florida Street
Baton Rouge, LA 70801

December 18, 1991

FAX: 202/260-0106

Dr. Peter Preuss
EPA - ORD, Director
Office of Technology Transfer
and Regulatory Support

Dear Dr. Preuss:

Enclosed is an expanded explanation of the information contained in Attachment 3 to D. R. Lynam's letter to you dated December 12, 1991. The information deals with differences in solubility/bioavailability of various manganese compounds. As you can see from the information, there is no reason to believe that the $R_fC$ for manganese underestimates the hazard associated with exposures to $Mn_3O_4$. If anything, the $R_fC$ overestimates the hazard.

If you have any questions, please call either Don Lynam at 504/388-8008 or me at 504/388-7565.

Sincerely,

Gerard D. Pfeifer

Gerard D. Pfeifer, Ph.D., CIH
Senior Research Associate

GDP:cr
cc: K. L. Fast - 202/778-2201 (FAX)
D. R. Lynam
Carl Mazza - EPA
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# Effect of Mixed Manganese Compounds on Toxicity

For a substance to be systemically toxic, it must be taken up by the body. Therefore, a substance must be bioavailable, that is, have the ability to cross biological membranes and enter the general circulation. At least for inorganic compounds, such as manganese oxides and salts, bioavailability is a function of solubility. In general, the more soluble a compound, the more bioavailable it is and therefore more likely to be able to produce adverse effects.

An excellent example of this involves the differences in solubility between lead oxide (PbO) and lead sulphide (PbS). Roy (1977) showed that workers exposed to the very insoluble lead sulphide had blood lead levels much lower than workers exposed to the rather soluble PbO at about the same levels.(1) The difference in uptake between PbO and PbS are a result of the difference in solubilities.

In general, manganese oxides are rather insoluble and are therefore are only poorly absorbed into the body. This led EPA to the conclusion that:

> "Obviously, insoluble manganese oxide is less toxic than several of the soluble compounds..."(2)

It is important to note that the terms "soluble" and "insoluble" are relative terms. Even though MnO, $Mn_2O_3$, $MnO_2$ and $Mn_3O_4$ are all listed as "insoluble" in handbooks (see attachment from CRC Handbook of Chemistry and Physics for example), some of these oxides are orders of magnitude more soluble than others. Some have more potential to be of biological importance than others. The solubilities or solubility product constants ($K_{sp}$) have been reported for several manganese oxides. These have been determined in well defined situations, i.e. distilled water, low ionic strength, specified pH and temperature, etc. which provide a measure of relative solubilities of these compounds.

The $K_{sp}$ data reported is as follows:(3)

$MnO + H_2O \rightarrow Mn(OH)_2 \rightleftharpoons Mn^{2+} + 2(OH)^-$ $K_{sp} = 2 \times 10^{-13}$

$MnCO_3 \rightleftharpoons Mn^{2+} + CO_3^{2-}$ $K_{sp} = 8.8 \times 10^{-11}$

$Mn(OH)_3 \rightleftharpoons Mn^{3+} + 3(OH)^-$ $K_{sp} = 1 \times 10^{-36}$

From these $K_{sp}$'s, we can calculate the molar concentration of these oxides in a saturated solution (solubility). The results are as follows:

| | |
|---|---|
| MnO | $1.1 \times 10^{-4}$ moles/liter |
| $MnCO_3$ | $9.4 \times 10^{-6}$ moles/liter |
| $Mn(OH)_3$ | $1.1 \times 10^{-8}$ moles/liter |

In addition, Swain et al.[4] has determined the solubility of $MnO_2$ to be $2 \times 10^{-6}$ moles/liter at pH 7.0, approximately the pH of blood (about 7.4). No data have been reported on solubility of $Mn_3O_4$.

If blood acted like distilled water in regard to the solubility of manganese oxides, saturated solutions of the compounds listed above would contain the following amounts of manganese:

| | |
|---|---|
| MnO | $Mn^{2+}$ 600 ug/dl |
| $Mn(OH)_3$ | $Mn^{3+}$ 0.06 ug/dl |
| $MnO_2$ | $Mn^{2+}/Mn^{3+}$ 11 ug/dl |

(Note: $Mn^{4+}$ is unstable and quickly becomes reduced in solution.)

These data show that MnO is 10,000 times more soluble than $Mn(OH)_3$, even though both are listed as insoluble.

The primary manganese oxide of interest is $Mn_3O_4$. The nominal valence of manganese in this compound is +2 2/3. A more accurate representation is $Mn^{2+}Mn_2^{3+}O_4$ or $MnO \cdot Mn_2O_3$. This compound exists in the solid state, but does not exist in solution. The crystal lattice must be broken down for solubilization to occur. Any $Mn_3O_4$ that ends up in solution does so only as MnO and $Mn_2O_3$. MnO and $Mn_2O_3$ would have to go into solution in equal molar quantities, that is, MnO could not go into solution selectively leaving $Mn_2O_3$ as a residue. Since $Mn_2O_3$ gives $Mn^{3+}$ in solution, and because $Mn^{3+}$ is much less soluble than MnO, the dissolution of $Mn_2O_3$ would be the limiting factor in the solubility of $Mn_3O_4$. It is also important to note that $Mn_3O_4$, as such, cannot enter the body and never appears as such in the body. Adverse effects of manganese must be a result of $Mn^{2+}$ or $Mn^{3+}$ and as we have seen, $Mn^{2+}$ (from MnO) may enter the body much more easily than $Mn^{3+}$ from oxides.

Therefore, $Mn_3O_4$ would be taken up slowly (as MnO and $Mn_2O_3$), if at all, from lung tissue. If inhaled, it would either (1) be deposited in the upper respiratory tract; (2) be deposited in the alveolar regions, or 3) be exhaled without being deposited. If the material is deposited in the upper respiratory regions, it would be removed by action of the mucocilliary elevator mechanism, enter the gut and would be handled as ingested material. That $Mn_3O_4$ deposited in the alveolar regions, being insoluble, would be engulfed by macrophages and removed. This material would also enter the gut and would be handled identically to ingested material.

For a substance to be systemically toxic, it must be taken up by the body. (Toxicologically speaking, the gut is external to the body.) As Loomis states in regard to the gastrointestinal tract: "Although it is within the body, its contents are essentially exterior to the body fluids. Therefore, chemicals in the gastrointestinal tract could produce an effect only on the surface of the mucosal cells that line the tract, unless absorption from the gastrointestinal tract took place."[5]

Because the amount of manganese ingested is many times that inhaled (3,000-5,000 ug ingested/day versus 1 ug inhaled/day assuming an average exposure of 0.05 $ug/m^3$), the inhaled manganese contributes virtually nothing to the body burden of manganese.

These conclusions have been borne out in several primate studies involving exposure to various manganese compounds by different routes. In general, manganese oxides can produce toxic effects only when large amounts are injected into the monkey.[6] Feeding and inhalation studies involving primates and massive doses of oxides of manganese have generally been negative.[7] A study involving feeding large quantities of various manganese compounds to rodents showed that soluble forms (chloride and acetate) caused adverse effects (decreased body weight gain, lowered red blood cell count) while insoluble forms (carbonate and dioxide) did not cause these effects.[8] These results strongly suggest that these insoluble compounds are unable to enter the body by normal routes. They also suggest that studies involving mixed manganese compounds may well overestimate the toxicity of insoluble manganese oxides, especially $Mn_3O_4$.

The Roels-Lauwerys study, on which the $R_fC$ was based, involved exposures to MnO, $MnO_2$, $Mn_3O_4$, $MnCO_3$, and $MnSO_4$ (which is very soluble). Detailed information from SEDEMA, included in Donald R. Lynam's letter to Peter Preuss of December 12, 1991, shows that most exposure was to MnO which is much more biologically available than $Mn_3O_4$. Therefore, there is no justification for believing that the $R_fC$ derived for "manganese" based on the Roels study underestimates the hazards of exposure to $Mn_3O_4$.

G. D. Pfeifer
December 18, 1991

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CRC

# HANDBOOK of CHEMISTRY and PHYSICS

61ST EDITION

1980—1981

CRC PRESS

## PHYSICAL CONSTANTS OF INORGANIC COMPOUNDS (Continued)

| No. | Name | Synonyms and Formulae | Mol. wt. | Crystalline form, properties and index of refraction | Density or spec. gravity | Melting point, °C | Boiling point, °C | Solubility, in grams per 100 cc: Cold water | Hot water | Other solvents |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Manganese** | | | | | | | | | |
| m124 | fluoride, di- | $MnF_2$ | 92.93 | red, tetr, or redsh powd | 3.98 | 856 | ... | $0.06^{40}$ | $0.48^{100}$ | s a; i al, eth |
| m125 | fluoride, tri- | $MnF_3$ | 111.93 | red cr | 3.54 | d | ... | d | d | s a |
| m126 | formate | $Mn(CHO_2)_2.2H_2O$ | 181.00 | rhomb | 1.953 | d | ... | s | s | ... |
| m127 | (II) glycerophosphate | $MnC_3H_7O_6P$ | 225.00 | wh or sl red powd | ... | ... | ... | sl s | ... | s a, citr a; i al |
| m128 | hydroxide | $MnO(OH)_2$ | 104.95 | blk-brn, amorph (exist ?) | 2.58 | ... | ... | v sl s | ... | ... |
| m129 | (II) hydroxide | Nat. pyrochroite, $Mn(OH)_2$ | 88.95 | wh-pink, trig 1.723, 1.681 | $3.258^{13}$ | d | ... | $0.0002^{18}$ | ... | s a, $NH_4$ salts; i alk |
| m130 | (III) hydroxide | Manganite, $MnO(OH)$ | 87.94 | br-blk, rhomb, 2.24, 2.24, 2.53 (Li) | 4.2–4.4 | d | ... | i | i | s HCl, h $H_2SO_4$ |
| m131 | iodide, di- | $MnI_2$ | 308.75 | pink, hex cr, deliq, br. in air | 5.0 | 638 (vac) d ca 80 | subl vac 500 | s | s | $0.02^{25}$ $NH_3$ |
| m132 | iodide, di-, tetrahydrate | $MnI_2.4H_2O$ | 380.81 | rose, monocl, deliq | ... | d | ... | s | v s | ... |
| m133 | hexaiodoplatinate | $MnPtI_6.9H_2O$ | 1173.59 | trig | 3.604 | d | ... | ... | ... | ... |
| m134 | (II) nitrate | $Mn(NO_3)_2.4H_2O$ | 251.01 | col. or rose, monocl | 1.82 | 25.8 | 129.4 | $426.4^0$ | ∞ | v s al |
| m135 | (II) lactate | $Mn(C_3H_5O_3)_2.3H_2O$ | 287.04 | pa red, monocl | ... | d | ... | 10 | v s | s al |
| m136 | (II) oxalate | $MnC_2O_4$ | 142.96 | wh cr powd | 2.43 | d 150 | ... | i | i | s a, $NH_4Cl$ |
| m137 | (II) oxalate, dihydrate | $MnC_2O_4.2H_2O$ | 178.98 | redsh-wh oct cr powd | ... | $-2H_2O$, 100 | d | $0.0312^{25}$ | $0.037^{100}$ | ... |
| m138 | (II) oxalate, trihydrate | $MnC_2O_4.3H_2O$ | 197.00 | pink, tricl | ... | $-H_2O$, 25 | ... | ... | ... | ... |
| m139 | (II, III) oxide | Nat. hausmannite, $Mn_3O_4$ | 228.81 | blk, tetr (rhomb), 2.46, (Li) 2.15 (Li) | 4.856 | 1564 | ... | i | i | s HCl |
| m140 | oxide, di- | Nat. pyrolusite, $MnO_2$ | 86.94 | blk, rhomb, or brn-blk powd | 5.026 | −O, 535 | ... | i | i | s HCl; i $HNO_3$, acet |
| m141 | oxide, hept- | $Mn_2O_7$ | 221.87 | dk red oil, hyg, exp | 2.396 | 5.9 | d 55, exp 95 | v s | d | s $H_2SO_4$ |
| m142 | (II) oxide, mon- | Nat. manganosite, MnO | 70.94 | grn, cub, 2.16 | 5.43–5.46 (3.7–3.9) | ... | ... | i | i | s a, $NH_4Cl$ |
| m143 | (III) oxide, sesqui- | Nat. braunite, $Mn_2O_3$ | 157.87 | blk, cub (tetr) | 4.50 | −O, 1080 | ... | i | i | s a; i ac a |
| m144 | oxide, tri- | $MnO_3$ | 102.94 | redsh, deliq (exist ?) | ... | d | ... | s | d | s alk, $H_2SO_4$ |
| m145 | (III) *meta*phosphate | $Mn_2(PO_3)_6.2H_2O$ | 619.74 | ... | ... | ... | ... | sl s | s | ... |
| m146 | (II) *ortho*phosphate | Nat. reddingite, $Mn_3(PO_4)_2.3H_2O$ | 408.80 | rose or yelsh-wh rhomb, 1.651, 1.656, 1.683 | 3.102 | ... | ... | ... | ... | ... |
| m147 | (III) *ortho*phosphate | $MnPO_4.H_2O$ | 167.92 | gray cr powd | ... | $-H_2O$, 300 | d | i | ... | s h conc $H_2SO_4$, conc HCl, molten $H_3PO_4$ |
| m148 | (II) *ortho*phosphate, di-H | $Mn(H_2PO_4)_2.2H_2O$ | 284.94 | ... | ... | $-H_2O$, >100 | ... | s | ... | i al |
| m149 | (II) *ortho*phosphate mono-H | $MnHPO_4.3H_2O$ | 204.97 | red, rhomb or pink powd, 1.656 | ... | ... | ... | sl s | d | s a; i al |
| m150 | (II) *pyro*phosphate | $Mn_2P_2O_7$ | 283.82 | br-pink, monocl, 1.695, 1.704, 1.710 | $3.707^{25}$ | 1196 | ... | i | ... | s a |
| m151 | (II) *pyro*phosphate, trihydrate | $Mn_2P_2O_7.3H_2O$ | 337.87 | wh, amorph powd | ... | ... | ... | i | ... | s $K_4P_2O_7$ sol, $H_2SO_3$; i acet |
| m152 | phosphide, mono- | MnP | 85.91 | dk gray | $5.39^{18}$ | 1190 | ... | i | i | sl s $HNO_3$ |
| m153 | (tri-)phosphide, di- | $Mn_3P_2$ | 226.76 | dk gray | $5.12^{18}$ | 1095 | ... | i | i | sl s dil $HNO_3$ |
| m154 | (II) *hypo*phosphite | $Mn(H_2PO_2)_2.H_2O$ | 202.93 | rose cr or powd | ... | $-H_2O$, >150 | ... | 12.5 | 16.7 | i al |
| m155 | (II) *ortho*phosphite | $MnHPO_3.H_2O$ | 152.93 | redsh | ... | $-H_2O$, 200 | ... | sl s | ... | s $MnSO_4$, $MnCl_2$ |
| m156 | selenate, dihydrate | $MnSeO_4.2H_2O$ | 233.93 | rhomb | 2.95–3.01 | ... | ... | s | s | ... |
| m157 | selenate, pentahydrate | $MnSeO_4.5H_2O$ | 287.97 | pa red, trig | 2.33–2.39 | ... | ... | ... | ... | ... |
| m158 | selenide | MnSe | 133.90 | gray, cub | 5.55 | ... | ... | i | ... | d dil a |
| m159 | selenite | $MnSeO_3.2H_2O$ | 217.93 | monocl cr | ... | ... | ... | v sl s | v sl s | ... |
| m160 | (II) *meta*silicate | Nat. rhodonite, $MnSiO_3$ | 131.02 | red, tricl, 1.733, 1.740, 1.744 | 3.72 | 1323 | ... | i | ... | i HCl |
| m161 | silicide, di- | $MnSi_2$ | 111.11 | gray, oct | 5.24 | ... | ... | d | i | s HF, alk; i $HNO_3$, $H_2SO_4$ |
| m162 | silicide, mono- | MnSi | 83.02 | tetrah | 5.90 | 1280 | ... | i | i | s HF; v sl s a |
| m163 | (di-)silicide | $Mn_2Si$ | 137.96 | quadr pr | 6.20 | 1316 | ... | i | i | s HCl, NaOH; i $HNO_3$ |
| m164 | (II) sulfate | $MnSO_4$ | 151.00 | redsh | 3.25 | 700 | d 850 | $52^0$ | $70^{70}$ | sl s al; i eth |
| m165 | (III) sulfate | $Mn_2(SO_4)_3$ | 398.06 | grn cr, deliq, hex | 3.24 | d 160 | ... | d | d | s HCl, dil $H_2SO_4$; i conc. $H_2SO_4$, $HNO_3$ |